REMARKS

Claims 54-58, 60 and 61 have been withdrawn from consideration by the Examiner. Claims 62 and 63 have been added. Support for Claims 62 and 63 is found throughout the application as originally filed, for example, at page 14, line 25 through page 15, line 5; and page 89, line 28 through page 90, line 23.

Claims 53-63 are pending. Claims 53, 59, 62 and 63 are currently under consideration.

Paragraph 8. Rejection of Claims 53 and 59 Under 35 U.S.C. § 103(a) as being obvious over Queen *et al.* (U.S. Patent No. 5,530,101) in view of Lazarovits *et al. (J. Immunol. 151*:6482-6489 (1993)) and further in view of Ringler *et al.* (U.S. Patent No. 6,551,593) and the art known 21/28'CL and GM6076'CL antibody sequences.

The rejection reflects the Examiner's mis-understanding of Federal Circuit precedent regarding the patentability of compositions of matter that are claimed using structural terms, when the prior art discloses methods that may be suitable for producing the claimed compositions of matter. In particular, the Examiner believes that the claimed humanized immunoglobulin or antigen-binding fragment thereof and compositions comprising same are obvious in view of the method for producing a humanized antibody disclosed by Queen *et al.*, the disclosure of the mouse Act-1 antibody and hybridoma by Lazarovitz *et al.* and Ringler *et al.*, and the art known 21/28'CL and GM6076'CL antibody sequences. In the Examiner's opinion, the claimed compositions of matter are obvious because the person of ordinary skill in the art would have been motivated to produce a humanized version of the mouse Act-1 antibody using the method of Queen *et al.*, and the starting materials in the other cited references, with a reasonable expectation of success.

Claims 53 and 59 are not obvious over of the cited combinations of references. Claims 53 and 59 recite that the humanized immunoglobulin or antigen-binding fragment comprises a heavy chain that comprises the variable region of SEQ ID NO:19 and a light chain that comprises the variable region of SEQ ID NO:21. The recited variable region sequences are not inherent in the murine Act-1 antibody, and the method of Queen *et al.* would not have "led inevitably" to the

variable regions of SEQ ID NOS:19 and 21. Accordingly, a *prima facie* case of obviousness has not been established. In addition, even if for the sake of argument only, there is some inference of obviousness, the previously provided evidence of unexpected results rebuts the inference and establishes patentability.

A. A *prima facie* case of obviousness has not been established.

The rejection is inconsistent with Deuel and Goldgaber, because the disclosure in the cited references does not establish a *prima facie* case and would not have "led inevitably" to the claimed compositions of matter. When novel compounds are claimed using structural terms, a *prima facie* case of obviousness requires that the prior art suggest the claimed compounds themselves to the person of ordinary skill in the art. In re Deuel, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995). The existence of a general incentive and techniques suitable to arrive at the claimed invention is not sufficient to establish a *prima facie* case. Id., at 216.

Deuel unambiguously articulates a fundamental rule of law for analyzing obviousness under 35 U.S.C. § 103: the existence of technology that is suitable for producing a novel composition does not on its own render that novel composition obvious. Id. at 1216. Therefore, Deuel controls the analysis in this application, even though the ultimate question of obviousness under § 103 is determined on the particular facts of this case. The Board of Patent Appeals and Interferences follows Deuel. For example, in Goldgaber the Board stated:

> We are mindful of the holding in Bell, and the recently issued opinion In re Deuel, ... reaffirming the principle that a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.

Goldgaber, 41 USPQ2d 1172, 1176 (Bd. Pat. App. & Inter. 1995).

In Deuel, the application at issue disclosed the purification and characterization of "heparin-binding growth factor" (HBGF) from bovine uterine tissue, and disclosed the amino acid sequence of the first 25 N-terminal amino acids of HBGF. In re Deuel, 34 USPQ2d at 1212. The application also disclosed the nucleotide sequence of a bovine and a human cDNA encoding HBGF. Id.

Claims drawn to nucleic acids encoding human heparin-binding growth factor were rejected by the Examiner under 35 U.S.C. § 103 as being obvious over a reference that disclosed the first 19 amino-terminal amino acids of a "heparin-binding brain mitogen" ("Bohlen") and a reference that described a method for isolating DNAs or cDNAs by screening a DNA or cDNA library with a gene probe ("Maniatis"). Id. at 1212-1214. The 19 amino acid sequence disclosed by Bohlen matched the first 19 amino acids of the N-terminal amino acid sequence disclosed in Deuel's application. Id. at 1213. The court reversed the rejection stating:

> Because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art.

Id. at 1214. The court further stated:

> A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. Thus, Maniatis's teachings, even in combination with Bohlen, fail to suggest the claimed invention.

Id. at 1216.

In Goldgaber, the Board distinguished Deuel and held that claims drawn to a nucleic acid which hybridizes to message for beta-amyloid polypeptide of Alzheimer's disease and which hybridizes with an oligonucleotide probe having a nucleotide sequence disclosed in Figure 1 of the application, were rejected as obvious over Glenner *et al.* (U.S. Patent No. 4,666,829; "Glenner") and Huynh *et al.* ("Huynh"). Ex parte Goldgaber, 41 USPQ2d at 1173. The Board, clearly mindful of Federal Circuit precedent, correctly set a high standard for distinguishing Bell and Deuel that focuses on the specific teachings of the cited references and the results that those teachings would inevitably produce. Id., at 1174-1177.

In Goldgaber, the primary reference, Glenner, disclosed the amino acid sequence of Alzheimer's Amyloid Polypeptide (AAP), the sequences of two sets of oligonucleotide probes suitable for isolating a gene that encodes AAP, methods for performing hybridization reactions, and use of the oligonucleotides in diagnostic assays. Id. at 1173. The oligonucleotide probes were said to be targeted to areas of low degeneracy in the AAP sequence, and designed to have the highest degree of specificity for the cDNA encoding AAP that could be attained under the

circumstances. (Glenner, at column 9, lines 30-62.) Huynh disclosed methods for constructing and screening cDNA libraries. Id. Figure 1 of Goldgaber's application included an illustration of the nucleotide sequence encoding beta-amyloid polypeptide and the amino acid sequence of the beta-amyloid polypeptide. Id. The amino acid sequence of the beta-amyloid polypeptide illustrated in Figure 1 of Goldgaber's application is the same as the amino acid sequence of AAP disclosed in Glenner. Id. See also, Glenner, at column 6.

The Board found that Glenner disclosed "clearly and unequivocally that it *is* possible to ascertain the base sequence of the gene coding for AAP, ... [and] the meaning [sic] for accomplishing that result, *i.e.*, two sets of fully degenerate probes." Id. at 1176. The Board also found that Glenner put the person of skill in the art in possession of the probes which it characterized as being the key to success. Id., at 1174. The Board found that the combined teachings of Glenner and Huynh "would have led inevitably to a clone of DNA meeting the limitations recited in claim 4," and stated that "Glenner puts the key in the lock of the door of success." Id., at 1175 (emphasis added).

The Board also found factual distinctions between the teachings of Glenner and Huynh and the teachings of the references in Bell and Deuel.

> Conspicuous by its absence from Rinderknecht or Bohlen [the primary references in Bell and Deuel, respectively] is any teaching relating to the DNA cDNA or the gene coding for the polypeptide of interest. Not only is the "primary" reference Glenner more comprehensive than the primary references in Bell or Deuel, but the "secondary" reference Huynh is also stronger than the secondary references in those cases.

Id., at 1176.

The Board affirmed the rejection under 35 U.S.C. § 103 and distinguished Deuel stating:

> The facts before us, however, present a different issue [than was presented in Deuel] and a more compelling case of obviousness because Glenner discloses more than the amino acid sequence of AAP. Glenner constructs a "bridge" of information leading from the polypeptide AAP via the oligonucleotides corresponding to its amino acid sequence to the gene coding for AAP.

Id. at 1177 (emphasis added).

> Glenner puts a person having ordinary skill in possession of two sets of fully degenerate probes, and Huynh discloses specific information pertaining to the construction and screening of a suitable cDNA library. The information in the Glenner patent, when combined with the Huynh reference, provide a reasonable expectation of success which is all that is required for obviousness under 35 USC 103.

Id. (emphasis added). Thus, the Board distinguished Deuel based upon the disclosure of oligonucleotide probes in Glenner, which provided a "bridge" of information that would have "led inevitably" to the claimed nucleic acid. The Board articulated a high standard for distinguishing Bell and Deuel that focuses on the specific teachings of the cited references, and the results that those teachings would have "inevitably" produced. Id., at 1174, 1177.

Like in Deuel, this application claims new chemical entities (*i.e.*, humanized immunoglobulin or antigen-binding fragment thereof) in structural terms by reciting the amino acid sequences of the heavy chain and light chain variable regions that make up the antigen-binding site, and none of the cited references contain any teachings that reasonably suggest the particular amino acid sequences that are recited in the claims. Deuel makes clear that incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. In re Deuel, 34 USPQ2d at 1216.

The facts of this application militate against a finding of obviousness more strongly than the facts in Deuel. In Deuel, the cited prior art disclosed a 19 amino acid sequence that matched the first 19 amino acids of the N-terminal amino acid sequence disclosed in Deuel's application. Id., at 1213. Arguably, all that remained was to isolate and sequence the claimed cDNA following the precise teachings of the Maniatis reference.

In this case, following the precise teachings of Queen *et al.* would not have "led inevitably" to the claimed immunoglobulin or antigen-binding fragment, because amino acid changes from the human acceptor amino acid to the mouse donor amino acid that are expressly taught by Queen *et al.* do not appear in the variable region amino acid sequences recited in the claims (variable regions of SEQ ID NOS:19 and 21).

Queen *et al.* teach that "a major problem with present humanization procedures has been a loss of affinity for the antigen, in some instances as much as 10-fold or more, especially when the antigen is a protein." (Queen *et al.* at column 2, lines 9-13. (Citations omitted).) The method of Queen *et al.* generally comprises replacing amino acid residues in a human "acceptor" variable region with amino acids found in a non-human "donor" variable region, and this method is said to provide a means for obtaining higher affinity humanized antibodies. (Id., at column 13, line 56 *et seq.*) In particular, Queen *et al.* describe five categories of amino acids found in a non-human "donor" variable regions. (Id., at column 13, line 66 through column 16, line 5.) Queen *et al.* expressly teach that "[p]referably, at many or all amino acid positions in one of these categories, the donor amino acid will in fact be selected [for inclusion in the humanized antibody rather than the amino acid from the human acceptor variable region]." (Id., at column 13, lines 63-65.)

In contrast to the express teachings of Queen *et al.*, the variable regions of SEQ ID NOS:19 and 21 contain certain acceptor amino acids at positions that Queen *et al.* teach should be occupied by non-human donor amino acids. For example, the light chain variable region amino acid sequence of SEQ ID NO:21 comprises a Met residue at position 4 of the mature light chain variable region (amino acid 24 of SEQ ID NO:21). As described in the application, this amino acid residue could have been replaced with Val which is present at position 4 of the mouse donor variable region. (Specification at page 78, lines 20-31.) In fact, the application teaches that the mean volume for Met at this position is higher than the mean volume for Val at this position and, therefore, retaining Met at this position could alter the conformation of CDRs 1 and 2 (L1 and L2 loops) and result in lower affinity for antigen. (Id.) Based on these teachings, and the teachings of Queen *et al.*, position 4 of the mature light chain variable region of SEQ ID NO:21 (amino acid 24 of SEQ ID NO:21) is a Category 4 position because the amino acid at this position is capable of interacting with amino acids in the CDRs. (Queen *et al.*, at column 14, line 39 through page 15, line 57.) Accordingly, the method of Queen *et al.* would not have "led inevitably" to variable region of SEQ ID NO:21, because Queen *et al.* call for the replacement of the Met at position 4 of the mature human acceptor light chain variable region (amino acid 24 of SEQ ID NO:21) with the Val residue of the donor mouse variable region.

Similarly, the heavy chain variable region amino acid sequence of SEQ ID NO:19 comprises an Arg residue at position 38 (amino acid 57 of SEQ ID NO:19), and an Ala residue at position 40 (amino acid 59 of SEQ ID NO:19). As described in the application, these residues are positioned underneath CDR2 (H2 loop) and pack close to 63Phe in CDR2. (Specification at page 80, lines 25-29.) The application further teaches that these amino acid residues could have been replaced with Lys and Arg which are present in the mouse donor variable region at positions 38 and 40, respectively. (Specification at page 32, lines 23-28.) Again, based on these teachings, and the teachings of Queen *et al.*, positions 38 and 40 of the mature heavy chain variable region of SEQ ID NO:19 (amino acids 57 and 59 of SEQ ID NO:19) are Category 4 positions, because the amino acids at these positions are capable of interacting with amino acids in the CDRs. (Queen *et al.*, at column 14, line 39 through page 15, line 57.) Accordingly, the method of Queen *et al.* would not have "led inevitably" to SEQ ID NO:19, because Queen *et al.* call for the replacement of the 38Arg and 40Ala of the mature human acceptor heavy chain variable region (amino acids 57 and 59 of SEQ ID NO:19) with Lys and Arg of the donor mouse heavy chain variable region, respectively.

In addition, SEQ ID NO:19 contains other human acceptor amino acids at positions that Queen *et al.* teach should be occupied by mouse donor amino acids. For example, there is an Arg at position 44 of the mature heavy chain variable region amino acid sequence (amino acid 63 of SEQ ID NO:19). As taught in the application, an Arg residue at this position is rare in human sequences, occurring in 5 of 48 human sequences examined. (Specification at Table 4.) Accordingly, position 44 (amino acid 63 of SEQ ID NO:19) is a Category 2 position as defined by Queen *et al.* (Queen *et al.*, at column 14, lines 1-26.) Similarly, there is an Ala at position 76 of the mature heavy chain variable region amino acid sequence (amino acid 95 of SEQ ID NO:19). Again, the application teaches that an Ala residue at this position is rare in human sequences, occurring in 4 of 50 human sequences examined. (Specification at Table 4.) Accordingly, position 76 (amino acid 95 of SEQ ID NO:19) is also a Category 2 position as defined by Queen *et al.* Because positions 44 and 76 of the mature heavy chain variable region (amino acids 63 and 95 of SEQ ID NO:19) are Category 2 positions, Queen *et al.* calls for replacing them with amino acids from the mouse donor variable region. This was not done in the variable region of SEQ ID NO:19.

Further, the variable region of SEQ ID NO:19 contains the human acceptor residue Arg at position 67 of the mature heavy chain variable region (amino acid 86 of SEQ ID NO:19). As taught in the application, this position is adjacent to CDR2 of the heavy chain variable region. Accordingly, position 67 (amino acid 86 of SEQ ID NO:19) is a Category 3 position as defined by Queen *et al.* (Queen *et al.* at column 14, lines 27-38.) Thus, Queen *et al.* call for the replacement of the human acceptor amino acid Arg at this position with the amino acid from the mouse donor variable region. Again, this was not done in the variable region of SEQ ID NO:19.

In view of the foregoing, it is clear that the teaching of Queen *et al.* would not have "led inevitably" to the claimed invention, because the variable regions of SEQ ID NOS:19 and 21 contain human donor amino acids at positions that Queen *et al.* expressly teach should be substituted with mouse donor amino acids. Therefore, the person of ordinary skill in the art could only have arrived at the claimed invention by disregarding the express teachings of Queen *et al.* that many or all of the human amino acids at positions that fall into the defined categories will be replaced with the non-human donor amino acid in the humanized variable region. (Queen *et al.*, at column 13, lines 63-65.)

Accordingly, this application is unlike Goldgaber, because it does not present facts that can be distinguished from Deuel. Critical to the Board's decision in Goldgaber was the disclosure in Glenner of the nucleotide sequences of two sets of oligonucleotide probes targeted to areas of low degeneracy in the AAP, methods for performing hybridization reactions, and use of the oligonucleotides in diagnostic assays. Ex parte Goldgaber, 41 USPQ2d at 1177. The Board viewed these teachings as forming a "bridge" of information that "led inevitably" to the claimed nucleic acid. Id. at 1174, 1177. There is no such bridge in this case. Thus, the rejection is inconsistent with Deuel and Goldgaber and should be withdrawn.

Reconsideration and withdrawal of the rejection is requested.

B. Surprising Results

The Examiner states that the claims are not commensurate in scope with the disclosed unexpectedly superior results disclosed in the specification, namely that LDP-02 is specific for the epitope recognized by murine Act-1, and that its binding affinity was better than that of the

murine antibody. (Specification at page 105, lines 25-27.) According to the Examiner, the claims are not commensurate in scope because they do not recite the constant region of the humanized immunoglobulin or antigen-binding fragment thereof, and Pritsch *et al.* teach that the constant region can have an effect on the binding affinity of an antibody.

It is pointed out that Pritsch *et al.* is a post filing date reference that does not demonstrate the state of the art or the knowledge of the person of ordinary skill in the art at the time the invention was made. In addition, the observations of Pritsch *et al.* are contrary to accepted dogma and published results demonstrating that antigen binding properties of an antibody are substantially due to the nature of the variable region, and that constant regions have little if any influence on antigen binding. Accordingly, Pritsch *et al.* alone does not provide a proper basis for the Examiner's opinion.

When the prior art contains references with conflicting teachings, each reference must be weighed for its power to suggest solutions to the person of ordinary skill in the art. In re Young, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). In weighing the suggestive power of each reference, the degree to which one reference might accurately discredit another must be considered. Id. "If, as a matter of law, the issue is in equipoise, the applicant is entitled to the patent." In re Oetiker, 24 USPQ2d 1443, 1447 (Fed. Cir. 1992) (concurring opinion of J. Plager).

Pritsch *et al.* describe observations made during a study in which binding of two antibodies (and particular antigen-binding fragments of the antibodies) that contained identical variable regions and different constant regions was assessed. Although the antibodies had identical variable regions, one contained an IgG1 constant region and the other contained an IgA constant region. Thus, the antibodies were of different isotypes. Pritsch *et al.* report that the antibodies bound to their cognate antigen with different affinities.

Pritsch *et al.* recognized that their findings are contrary to accepted dogma in the field of immunology that antigen binding properties of an antibody are substantially due to the nature of the variable region, that constant regions have little if any influence on antigen binding, and that isotype switching is not a mechanism for enhancing the affinity of antibodies. Apparently mindful that their results may be an anomaly, Pritsch *et al.* refer to their observations as a "phenomenon" and state that it is unclear whether their observations of altered affinity upon

isotype switching could be an "unusual mechanism" for increasing affinity of antibodies. (Pritsch *et al.* at page 2242, right column.) Pritsch *et al.* also state that further work with other antibody-antigen pairs is needed to determine the frequency with which their results might occur. (Id.)

Indeed, the observations reported by Pritsch *et al.* are contrary to accepted convention and the published results of similar studies. For example, Shaw *et al.* describe the results of a study in which binding of four chimeric antibodies to antigen was measured. (Copy provided with the Supplemental Information Disclosure Statement (SIDS) filed concurrently herewith.) In this study, the chimeric antibodies tested contained the same variable region (derived from mouse 17-1A antibody) but different constant regions. (Shaw *et al.*, Abstract and Antibody Preparations.) The constant regions were IgG1, IgG2, IgG3 and IgG4. (Id.) Shaw *et al.* report that their study revealed that the "[m]ouse 17-1A and the four chIgG [chimeric IgG antibodies] bound similarly to two human colon cancer cell lines and had comparable binding affinities." (Shaw *et al.*, Abstract.)

Here, the Examiner has identified a reference that conflicts with accepted dogma and published results showing that antibodies that differ only in the constant region have comparable binding affinities. Thus, each reference, and the body of knowledge in the field, must be weighed for its power to suggest solutions to the person of ordinary skill in the art. In re Young, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). In this case, because there is no corroborating evidence to show that the observations of Pritsch *et al.* are genuine, or generally applicable to antibodies, it is improper to conclude that Applicants' surprisingly superior results can only support the patentablity of an antibody or antigen-binding fragment with a specified constant region.

Further, the teachings of Shaw *et al.* cast serious doubt on the teachings of Pritsch *et al.* and the general applicability of their observations. Accordingly, the objection to the scope of the claims vis-a-vis the unexpectedly superior results disclosed in the specification should be withdrawn.

The Examiner's attention is also directed to the additional evidence of surprising results in the record. In particular, the Examiner's attention is directed to the Declaration of Steven B. Landau, M.D. under 37 C.F.R. § 1.132 (Declaration) filed on January 31, 2000, which describes a Phase I clinical study of LDP-02 (an antibody of the invention described in Examples 2-4 of the

application). The study revealed that LDP-02 has unexpected pharmacokinetic and pharmacodynamic properties. For example, no free α4β7 binding sites (i.e., LDP-02 epitopes) were detected for about two weeks following a single administration of LDP-02 at the lowest dose tested (0.15 mg/kg)(see Declaration at the Figure). Administration of LDP-02 at higher doses (e.g., 2.5 mg/kg) resulted in saturation of α4β7 that persisted for up to 70 days (about four half lives). The remarkably persistent saturation of α4β7 by LDP-02 has a relationship to the pharmacokinetic half life of the antibody after a single administration (14-17 day *in vivo* half life when administered at 1.5 mg/kg or 2.5 mg/kg; see Declaration at Table 2 (t 1/2z)). The pharmacodynamic effect of maximal saturation up to 70 days in combination with pharmacokinetics results was unexpected and could not have been predicted at the time the invention was made.

Further evidence of the unexpected nature of the pharmacodynamic properties of LDP-02 is provided by the original design of the study itself. The study was originally designed to include blood sampling up to study day 36. However, as α4β7 saturation was still observed at this time point, the study was extended to include blood sampling up to day 212, when the amount of free α4β7 sites on lymphocytes returned to pre-dose levels. The unexpected results of the study indicate that LDP-02 may be therapeutically administered as a single dose at intervals of 2 weeks to 2 months or more in order to provide effective treatment.

The Examiner attention is also directed to Feagan S.B. *et al.*, *Gastroenterology*, *118*(4):A874 (2000), (Reference AU5 of record) which presents evidence of therapeutic efficacy of the claimed humanized immunoglobulin. Feagan *et al.* describe the results of a clinical study in which an antibody of the present invention (LDP-02, see Specification, Example 4 at page 90 *et seq.*) was administered to patients with moderately severe ulcerative colitis. Effectiveness measurements were collected during the study. Feagan *et al.* report that "40% of Group 3 patients [single administration of LDP-02 at 0.5 mg/Kg IV] had a complete endoscopic (modified Baron's score = 0) and clinical (MCS = 0) remission" (Feagan *et al.* at lines 37-38 of the abstract).

Further evidence of clinical efficacy is provided by Feagan *et al., N. Engl. J. Med.*, 352:2499-2507 (2005). (Copy provided with SIDS filed concurrently herewith.) This reference discloses the results of a multicenter, double-blind, placebo-controlled trial of LDP-02 (referred

to as MLN-02 in the reference) in patients with active ulcerative colitis. The authors report that "[t]wenty-eight percent of patients receiving 0.5 mg per kilogram and 12 percent of those receiving 2.0 mg per kilogram had endoscopically evident remission, as compared with 8 percent of those receiving placebo." (Feagan *et al.* (2005), Results.)

Each of the foregoing results individually is sufficient to rebut any presumption of obviousness, and when considered together clearly establish the patentability of the full scope of Claims 53 and 59.

Reconsideration and withdrawal of the rejection is requested.

Paragraph 10. Rejection of Claims 53 and 59 Under 35 U.S.C. § 103(a) as being obvious over Queen *et al.* (U.S. Patent No. 5,530,101) in view of Lazarovits *et al. (J. Immunol. 151*:6482-6489 (1993)) and further in view of the art known 21/28'CL and GM6076'CL antibody sequences as evidenced by Tiisala *et al.* or Mawhorter *et al.* or Yuann *et al.* or Schultz *et al.* or Nieto *et al.*

The rejection is substantially the same as the Paragraph 8 rejection, except the Examiner states that the evidentiary references disclose the public availability of the Act-1 hybridoma.

Claims 53 and 59 are not obvious for the reasons set forth with respect to the Paragraph 8 rejection, because even if the evidentiary references show public availability, the person of ordinary skill in the art would not have been "led inevitably" to the claimed compositions by following the teachings of Queen *et al.* In addition, even if for the sake of argument only a *prima facie* case of obviousness has been established, the record evidence of surprisingly superior results is sufficient to rebut any inference of obviousness. Reconsideration and withdrawal of the rejection are requested.

Paragraph 12. Rejection of Claims 53 and 59 Under 35 U.S.C. § 103(a) as being obvious over Queen *et al.* (U.S. Patent No. 5,,530,101) in view of Lazarovits *et al. (J. Immunol. 151*:6482-6489 (1993)), Springer *et al.* (Leucocyte Typing V), Retell *et al.*, Huston *et al.* (U.S. Patent No. 5,258,498) and further in view of the art known 21/28'CL and GM6076'CL antibody sequences.

The rejection is substantially the same as the Paragraph 8 rejection, except the Examiner relies on Springer *et al.*, Retell *et al.* and Huston *et al.* as disclosing the public availability of the Act-1 antibody and methods for amino acid sequencing.

Claims 53 and 59 are not obvious for the reasons set forth with respect to the Paragraph 8 rejection, because even if Springer *et al.*, Retell *et al.* and Huston *et al.* disclose the public availability of the Act-1 antibody and methods for amino acid sequencing., the person of ordinary skill in the art would not have been "led inevitably" to the claimed compositions by following the teachings of Queen *et al.* In addition, even if for the sake of argument only a *prima facie* case of obviousness has been established, the record evidence of surprisingly superior results is sufficient to rebut any inference of obviousness. Reconsideration and withdrawal of the rejection are requested.

Request for Rejoinder of Claims 54-56

Applicants request that Claims 54-56, drawn to methods that employ the humanized immunoglobulin or antigen-binding fragment thereof defined in Claim 53, be rejoined if Claim 53 is found to be allowable.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Acknowledgment of consideration of the SIDS is requested in the next Office Communication.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Robert H. Underwood

Robert H. Underwood
Registration No. 45,170
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
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